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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/081,309 | 02/21/2002 | Michael Brandt | 20859 | 3846 |

151 7590 07/27/2007

HOFFMANN-LA ROCHE INC.
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| EXAMINER | |
|---|---|
| CHANDRA, GYAN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 07/27/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/081,309 | BRANDT ET AL. | |
| | Examiner | Art Unit | |
| | Gyan Chandra | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *6/4/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3 and 5-15* is/are pending in the application.

4a) Of the above claim(s) *3,7 and 9-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-6, 8 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Re: Brandt et al.

Date of Priority: 2/21/2002(US 10/081,309)

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/4/2007 has been entered.

**Status of Application, Amendments, And/Or Claims**

Claims 1, 3 and 5-15 are pending.

Claims 3, 7 and 9-11 are withdrawn.

Claims 1, 5-6, 8 and 12-15 are under examination.

### *Response to Arguments*

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of

each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5-6, 8, and 12-13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Date et al (Oncogene, 17:3045-3054, 1998) in view of Bartley (US Patent No. 5,766,581) for the reasons of record on pg. 3-5 of the office action mailed on 7/26/2006.

The claims are drawn to a conjugate consisting of a NK4 molecule and a PEG having (i) a molecular weight of about 30-40 KDa and has formula –CO-(CH2)x-(OCH2CH2)mOR, (ii) wherein –CO group of said PEG forms an amide bond with one of the amino groups of the N-terminal fragment of said NK4, (iii) wherein X is 2or 3; m is from 450 to about 950; R is (C1-C6) alkyl, (iv) wherein said PEG is selected from monoethoxy polyethylene groups, (v) wherein the PEG is selected from the group of linear PEG and branched PEG chains, (vi) a pharmaceutical composition comprising said conjugate and at least on pharmaceutically acceptable carrier, and (vii) a composition comprising mono-pegylated NK4 conjugates wherein the PEG groups are attached to groups selected from the lysine side chains or to the N-terminal amino groups of NK4 molecules.

Applicants reiterate their previous arguments (filed on 4/2/2007) that (i) the reference Bartley only teaches pegylation of megakaryocyte growth and development factors (MGDFs) and related proteins, and that (ii) there is no apparent teaching of peg-modification of any unrelated protein to MDGF. Applicants argue that (iii) the reference Bartley discloses that the polymer/GFDF may have additional activities, enhanced or reduced as compared to the non-derivatized molecule, therefore, applicants argue that (iv) the art of pegylation is unpredective. Applicant argues that Bartley must be read in its entirety which teaches that "modification of the biological properties is unpredictable from the art."

Applicant's arguments regarding the reference Bartley that the refence does not teach pegylation of any other other protein have been fully considered but they are not persuasive because Bartley et al

teach that pegylation has been used in the preparation of therapeutic protein products, for example, Adagen® which is PEGylated adenosine deaminase is approved for treating severe immunodeficiency disease; PEGylated superoside dismutase for treating head injury; pegylated alpha interferon for treating hepatitis and many more (col. 5, lines30-37). and further because it is routine in the art to pegylate proteins as stated by Francis et al (previously presented,1998), **pegylation is a well established technique for the modification of therapeutic peptides and proteins** (pg. 2, under title: PEGylation of proteins and peptides). Francis et al emphasize that surprisingly, the pegylation is a single technique that overcomes with many of the pharmacological and toxicological problems of proteins and peptides (pg. 2, left column). Reddy on page 919, left column(IDS, 2000) states, "pegylation is well developed process" for modifying proteins. Reddy suggests that pegylation of a molecule typically results in different physicochemical properties than those of the parent moleuclue but Reddy emphasizes that **the key to generating pegylated proteins with important therapeutic action is the optimization of the process to produce a therapeutic drug with the desired pharmacologic characteristics** (page 919, left column). Reddy teaches that pegylated proteins have enhanced pharmacologic and pharmacodynamic properties compared to unmodified proteins (pg, 919, right column). Thus, Reddy and Francis teach that the pegylation of proteins is an established technique and that one skill in the art may need to optimize the pegylation of a specific protein for a desired outcome. Therefore, the rejection is maintained.

Claims 14 and 15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Date et al and Bartley et al as applied to claims 1-2, 4-6, 8, and 12-13 above, and further in view of Veronese et.al. (US Patent 6,528,485) for the reasons of record on pages 5-6 of the office action mailed on 7/26/2006.

Applicants do not argue this rejection.

Therefore, the previous arguments of 4/30/2007 are maintained.

***Conclusion***

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gyan Chandra
Art Unit 1646
11 July 2007
Fax: 571-273-2922

/Robert S. Landsman/
Primary Examiner, Art Unit 1647